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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,220	11/09/2001	Che-Kun James Shen	514162000120	5165

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,220	SHEN, CHE-KUN JAMES	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 08/01/05 has been acknowledged.

Claims 21-34 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 21, 23-27 and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record on PTO 1449*), for the same reasons of record as set forth in the office action mailed on 05/03/05.

The scope of invention as claimed encompasses an isolated cell comprising a transcriptional start site a promoter operably linked to the start site and an enhancer operably linked to the promoter, wherein the enhancer comprises the nucleotide sequences of SEQ ID NO:1. The scope of invention as claimed further encompasses a cell wherein the promoter (ζ–globin promoter) drives the transcription of a polypeptide (growth hormone).

Zhang teaches that HS-40 consists of multiple nuclear factor binding motifs that are occupied *in-vivo* in an erythroid lineage and developmental stage-specific manner. The cited art further teaches systematically analysis and functional roles of these factor-binding motifs of HS-40 by site-directed mutagenesis and transient expression assay in erythroid cell cultures. The cited art teaches that three of these HS-40 enhancer motifs, 5`NF-E2/AP1, GT II, and GATA-1(c), positively regulate the ζ-globin promoter activity in embryonic/fetal erythroid K562 cells and the adult α-globin promoter activity in adult erythroid MEL cells. The cited art further teaches that on the other hand, the 3`NF-E2/AP1 motif is able to exert both positive and negative regulatory effects on the ζ -globin promoter activity in K562 cells, and this dual function appears to be modulated through differential binding of the ubiquitous AP1 factors and the erythroid-enriched NF-E2 factor (page 8561, abstract). The cited art further teaches an expression vector comprising, a tissue specific ζ-globin promoter operably linked

to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). The cited art further teaches transfection of host cell using at least 10μg of plasmid construct that inherently incorporated 5-15 copies of transgene. The cited art further teaches a HS-40 enhancer element (NF-E2/AP1-II) which comprises the nucleotide sequence of SEQ ID NO:1 (**tctgagtca**) see page 8503, fig-1B, 3'NF-E2/AP1-II. The cited art further teaches a method of expressing p-HS40 (3'NF-E2/AP1-II)-ζ597GH expression vector into isolated K562 erythroid cells. The genetically modified K562 cells were transfected with expression vector and the expression of growth hormone was measured by GH assay and/or RNA primer extension assay (page 8503 fig 1 and 2). The cited art further teaches that mutant HS-40 enhancer comprises a 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) that exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3). Thus the cited art clearly anticipate the invention as claimed.

Response to arguments

The applicant arguments regarding prior art issue on pages 4-5 of respone filed on 08/01/05 has been fully considred. The applicant argues the invention as claimed is not anticipated by Zhang 1995 reference, since the cited art only teaches transient transfection of the DNA constructs which is considered not stable intergration of the DNA constructs into cellular chromosomes. The applicant furhter argues that the cited reference uses transient transfection to avoid the confounding effects of the position effects on gene expression that might result from chromosomal intergration. The applicant argues that in order to anticipate a claim the prior art must teaceh each and every limitation of claimed invention. However, applicant's argumetns are found not persuasive because the cited art clealry teaches the transfection of the genetic construct comprising SEQ ID NO:1 (tctgagtca) into host cells. Furthermore even though the cited art suggested the transient trenafection of genetic material it is known in the art that transfection of plasmids into host cells often results in the chromosomal intergration of genetic material transfected in the cells, which could be easily detected upon the selection of genetically modified cells. Thus given the broadest reasonable interpretation the cited art clealry anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

Claims 22, 28-29 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record on PTO 1449)* as applied to claims 21-27 and 30-32 above, and further in view of Zhang et al (Mol Cell Biol. 4:2298-308, 1993, *ref of record on PTO 1449*) , for the same reasons of record as set forth in the office action mailed on 05/03/05.

Zhang (1995) is discussed detail above. Even though Zhang inherently teaches an expression vector comprising a 373 bp fragment of HS40 enhancer region, which contain a mutated HS-40 enhancer element (NF-E2/AP1-II) comprising the nucleotide sequence of SEQ ID NO:1 (**tctgagtca**), Zhang does not teach nucleic acid sequences comprising SEQ ID NO:2 and SEQ ID NO:3 of instant application.

Zhang 1993 teaches a nucleotide sequence for HS-40 enhancer element which matches to the nucleotide sequences of SEQ ID NO:2 and SEQ ID NO:3 (page 2299, fig-1B). The cited art specifically teaches mutated HS-40 enhancer element (NF-E2/AP1) which comprises the nucleotide sequence of SEQ ID NO:1 (page 2304, col.1 fig-7A). In addition the cited art teaches transcriptional activation of human embryonic zeta 2 globin gene and the fetal/adult alpha-globin gene is mediated by erythroid cell-specific and developmental stage-specific nuclear factor-DNA complexes, which form at the enhancer (HS-40) and the globin promoters. Furthermore in view of prior art that teaches genetic modification of human and Hela cells, the transfection of other animal cells is obvious if not anticipated in view of cited prior art of record

Thus it would have been obvious that genetically modified embryonic/fetal erythroid K562 and adult erythroid MEL cells as disclosed by Zhang (1995) inherently comprises an expression vector that contains a **tctgagtca** mutated cited in the HS40 enhancer element of Zhang (1993). Alternatively it would have been obvious to use the flanking regions around the **tctgagtca** element, since HS-40 consists of multiple nuclear factor binding motifs that are occupied *in-vivo* in an erythroid lineage and developmental stage-specific manner. One would have been motivated to include the flanking regions around the **tctgagtca** element in order to regulate erythroid developmental in a stage-specific fashion. One would have a reasonable expectation of success because the genetic modification of HS40 enhancer elements by site directed mutagenesis has been well known in the art at the time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments

The applicant arguments regarding prior art issue on pages 5-7 of respone filed on 08/01/05 has been fully considred. The applicant argues that combination of cited art fails to teaceh or suggest that the transgene construct has been intergrated in the chromosome. This is found not persuasive because as stated above the the cited art clealry teaches the transfection of the genetic construct comprising SEQ ID NO:1 (tctgagtca) into host cells. Furthermore even though the cited art suggested the transient trenafection of genetic material it is known in the art that transfection of plasmids into host cells often results in the chromosomal intergration of genetic material transfected in the cells. The applicant further argues that the cited art teaches away from the invention as claimed, therefore one would not be motivated to modify these references to provide transfectants in which the DNA constuct are chromosomally intergrated. However this has been found not persuasive because as stated above the chromosomal integration is an inherent property of a transfection procedure. Therefore the cited art does not teach away from the invention as claimed but clearly anticipate the subject matter as claimed. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (See MPEP 2144). In instant case even if the cited art teaches genetic material that has not been integrated into a chromosome, it is obvious to select transfected cell having chromosomally integrated transgene with a reasonable expectation of success. The applicant furhter argues that Zhang 1993 teaches away from the invention because the

cited art stare that the point mutation TCTGAGTCA results in reduced expression by approximately 70% as compared to wild type sequences. The applicant argues that such reduction would discourage one skill in the art from employing this sequence to achieve the expression of target cells. However this is found not persuasive because Zhang 1995 clealry teacehs that mutant HS-40 enhancer comprising a 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) that exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3). Therefore applicant's arguments that one skilled in would be discouraged to employ such sequences is misplaced in view of Zhang 1995, who teacehs upregulation of transgene expression in the pesence of point mutation TCTGAGTCA. Thus the invention as claimed is prima facie obvious in view of cited prior art of record for the same reasons of record as set forth in the earlier office action.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If

attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

-sk

SUMESH KAUSHAL
PATENT EXAMINER